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The Treatment of Patients With Irritable Bowel Syndrome: Review of the Latest Data From the 2010 DDW Meeting

A Review of Selected Presentations From
the 2010 Digestive Disease Week
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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with irritable bowel syndrome.

Statement of Need/Program Overview: The Abstract Review Monograph will discuss the most recent updates emerging in treatment of patients with irritable bowel syndrome. An abundance of new data has recently come to light and will be presented at the 2010 DDW (Digestive Disease Week) convention in the treatment of patients with IBS. A distinct educational need exists in the gastroenterology community for an updated understanding of the latest treatment strategies.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Review the recent data on the treatment of patients with IBS.
2. Identify factors that may affect the development of IBS.
3. Describe the potential causes of IBS, diagnosis, and their effect on treatment selection.
4. Identify the medical options for direct treatment of IBS to relieve symptoms such as bloating, abdominal pain, constipation, diarrhea, and flatulence.

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Irritable Bowel Syndrome Abstract Review: The 2010 DDW Meeting

AST-120 for IBS

S1298: AST-120 (Spherical Carbon Adsorbent) Improves Pain and Bloating in a Randomized, Double-Blind, Placebo-Controlled Trial in Patients With Non-Constipating Irritable Bowel Syndrome (IBS)[1]

Jan F. Tack, M. S. Harris, Scott Proksch, Jeffrey D. Bornstein, Philip B. Miner

AST-120 is an oral, non-absorbed, carbon-based adsorbent that has been used safely in more than 360,000 Japanese patients and studied in patients with chronic kidney disease,[2] Crohn's disease,[3] and type 2 diabetes.[4] Mechanistically, it is reported to adsorb substances implicated in the pathogenesis of irritable bowel syndrome (IBS), including bacterial toxins and bile acids.[5] Tack and colleagues conducted a randomized, double-blind, placebo-controlled trial to determine the safety and efficacy of AST-120 in diarrhea-predominant or alternating IBS patients. The primary objective of this study was to measure the proportion of patients with IBS who responded to AST-120 therapy.

Upon enrollment in this study, a total of 115 patients underwent a 2-week run-in period and were then randomized to receive either 2 g of AST-120 (n=56) or a placebo (n=59) 3 times a day for 8 weeks. The 2 cohorts were matched for age, sex, IBS subtype, pain severity, bloating severity, stool frequency, and stool consistency. After the 8-week randomized treatment period, all participants were given a placebo for a 2-week washout period, followed by an 8-week phase of AST-120 treatment. Patients were considered responders if they had a reduction of 50% or more in days with pain over the previous 2 weeks of treatment compared to the run-in period. Pain severity and bloating severity were also measured using 100 mm visual analog scales.

Significantly more patients taking AST-120 responded at week 4 of the randomization period compared to those receiving a placebo (27% vs 10%; *P*=.029), regardless of gender or IBS subtype. After 8 weeks of treatment, these response rates increased to 32% and 25%, respectively. Over the course of the 8-week randomized phase, 21% of patients receiving AST-120 responded versus 11% of patients given a placebo. Other outcomes reported by the investigators were the mean reduction in bloating severity at week 2 (13 mm vs 2 mm; *P*=.007) and week 4 (14 mm vs -1 mm; *P*=.002), as well as pain severity reductions at week 4 (mean, 11 mm vs 6 mm) for patients treated with AST-120 and placebo, respectively. Compared to patients given a placebo, more patients treated with AST-120 had at least a 1-point improvement in stool consistency, and their IBS symptoms had a reduced impact on daily activities. Benefits achieved with AST-120 abated during the washout period but resumed upon restarting AST-120 therapy.

Overall, AST-120 was tolerable, with more than 85% of patients in both groups completing the 8-week randomization phase. Additionally, fewer patients in the AST-120 group reported 1 or more adverse events than those in the placebo group. Based on these findings, the authors of the study concluded that AST-120 is safe and well-tolerated while also reducing pain and bloating in patients with diarrhea-predominant and alternating IBS. As such, larger studies of AST-120 in IBS are warranted.

Rifaximin Double-blind Study for IBS

475i: Rifaximin Treatment for 2 Weeks Provides Acute and Sustained Relief Over 12 Weeks of IBS Symptoms in Non-Constipated Irritable Bowel Syndrome: Results From 2 North American Phase 3 Trials (TARGET 1 and TARGET 2)[6]

Mark Pimentel, Anthony Lembo, William D. Chey, Yehuda Ringel, Salam Zakko, Shadreck M. Mareya, Audrey L. Shaw, Jing Yu, Enoch Bortey, William P. Forbes

Rifaximin is an oral, gastrointestinal (GI)-selective antibiotic that is approved by the US Food and Drug Administration (FDA) for the reduction in risk of overt hepatic encephalopathy recurrence in patients at least

Table 1. Responders to Adequate Relief of IBS Symptoms and IBS-related Bloating (ITT Population)

Endpoints	TARGET 1 (N=623) (Rifaximin vs Placebo)	TARGET 2 (N=637) (Rifaximin vs Placebo)	Results of Pooled Data (N=1,260) (Rifaximin vs Placebo)
Adequate Relief of IBS Symptoms	40.8% vs 31.2% (*P*=.0125)	40.6% vs 32.2% (*P*=.0263)	40.7% vs 31.7% (*P*=.0008)
Adequate Relief of IBS-related Bloating	39.5% vs 28.7% (*P*=.0045)	41.0% vs 31.9% (*P*=.0167)	40.2% vs 30.3% (*P*=.0002)

IBS=irritable bowel syndrome; ITT=intent-to-treat.

18 years of age and for travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in patients older than 12 years of age. Ongoing studies are currently investigating rifaximin in IBS. A recent phase IIb multicenter clinical trial found that rifaximin effectively provided relief of global IBS symptoms such as bloating and improved quality of life in patients with diarrhea and mixed IBS.[7,8] Here, 2 identically designed phase III, randomized, double-blind, placebo-controlled, multicenter clinical trials (TARGET 1 and TARGET 2) evaluated the efficacy of rifaximin in nonconstipated IBS patients.

In these 2 phase III studies, a total of 1,260 patients (TARGET 1, n=623; TARGET 2, n=637) with mild-to-moderate symptoms of nonconstipated IBS symptoms were randomized to receive 550 mg of rifaximin 3 times a day or a placebo for 2 weeks. Responses were measured during a 10-week follow-up period, with the primary endpoint being the percentage of patients who were responders in the intent-to-treat (ITT) population. Patients were considered responders if they had adequate relief of weekly IBS symptoms for 2 or more of the first 4 weeks immediately following the 2-week treatment period. The rifaximin and placebo groups did not differ in terms of baseline demographics in the TARGET 1, TARGET2, or pooled study analyses. A significantly greater percentage of patients in the rifaximin group were responders compared with the placebo group in both TARGET trials and in the pooled analysis. In addition, a significantly higher proportion of patients taking rifaximin had IBS symptom relief compared to patients given a placebo (Table 1; TARGET 1, *P*=.0125; TARGET 2, *P*=.0263; Pooled, *P*=.0008). Adequate relief of bloating, a key secondary endpoint, was also met by significantly more patients in the rifaximin group compared to the placebo group (Table 1; TARGET 1, *P*=.0045; TARGET 2, *P*=.0167; Pooled, *P*=.0002). Patients taking rifaximin also had significantly improved daily assessments of IBS symptoms, bloating, abdominal pain, and discomfort, all of which were additional secondary endpoints. As independent studies and in a pooled analysis, TARGET 1 and TARGET 2 both reported a significantly higher likelihood of sustained IBS symptom relief during the 3-month study period in patients taking rifaximin compared to those given a placebo. Additionally, the safety profile of rifaximin was similar to the placebo.

Based on the combined results of TARGET 1 and TARGET 2, the authors concluded that 550 mg of oral rifaximin taken 3 times daily for 14 days is significantly more effective than placebo in achieving adequate relief of IBS symptoms. Furthermore, rifaximin is significantly more likely to provide acute and sustained symptom relief of IBS symptoms over a 12-week period.

Patients Not Responding to Antibiotics Have Secondary Causes of Symptoms

S1326: Presumed IBS Subjects With Short Remission After Antibiotic Therapy Often Have Secondary Causes for Their Symptoms[9]

Jim Y. Chou, Robert Tabrizi, Mark Pimentel, Thomas Sokol

Antibiotics have been used to treat IBS since the early 2000s, when small intestinal bacterial overgrowth (SIBO) identified by lactulose breath testing (LBT) was observed in patients with IBS; SIBO was subsequently suggested as a causative factor for IBS.[10,11] Although multiple randomized, controlled trials have supported the use of antibiotics in IBS, no single antibiotic has yet been FDA-approved for IBS.[11-13] It is reported that with the increased use of antibiotics, a shift in reasons for tertiary care referrals of antibiotic-naïve patients with IBS and patients with IBS who are refractory to

antibiotics has occurred.[9] In this study, the investigators performed a chart review of patients with IBS and abnormal LBT results who were referred to a GI motility program at a tertiary care medical center after having poor responses to antibiotics (ie, response lasting <1 month). Patients included in this analysis had abnormal LBTs and antibiotic responses lasting less than 1 month. The goal of the study was to determine whether diagnoses or explanations other than SIBO could be identified for these patients' abnormal breath test results and short antibiotic-induced remission periods.

Of the 65 patients who met the criteria for the study, alternative explanations for abnormal LBT results and early relapse were identified for 20 (30.8%) of them. Alternative diagnoses identified by the investigators included small bowel obstruction (n=2), rectocele/prolapse (n=3), intestinal malrotation (n=1), small bowel diverticular disease (n=2), and volvulus (n=1). These patients were all referred for surgical treatment. Other factors contributing to SIBO and short remission periods were chronic narcotic use (n=3), neuropathic causes (eg, Addison's disease [n=1], scleroderma [n=1], colonic inertia [n=1] or vagotomy from laryngeal tumor surgery [n=1]), and inflammatory diseases (eg, ulcerative colitis [n=1] and NSAID-induced intestinal ulceration [n=1]). Unusual causes included mitochondrial myopathy, atrophic gastritis, and vitamin B_{12} deficiency. Based on these findings, the authors concluded that as the number of presumed IBS subjects treated with antibiotics increases, the number of referrals to tertiary care centers based on response failure rates to antibiotics will also increase.

Otilonium Bromide for IBS

S1297: Otilonium Bromide Improves Symptoms and Delays Time to Post-Treatment Relapse in Irritable Bowel Syndrome Patients[14]

Jan F. Tack

Spasmolytic, serotonergic, and antidiarrheal agents are all commonly used to manage IBS symptoms. However, relapse of IBS symptoms is common upon discontinuation of therapy.[15] Otilonium bromide, which blocks intestinal and colonic L-type calcium channels, is safely and effectively used to manage abdominal pain and diarrhea worldwide.[15] When compared with a placebo, otilonium bromide significantly reduced the frequency and severity of pain episodes in patients with IBS in several randomized, controlled clinical trials.[16,17] An extended analysis of one of these studies also found that otilonium bromide was superior to a placebo in reducing abdominal distension, diarrhea, or constipation severity, and mucus levels in stools.[18] Otilonium bromide is well-tolerated, which is likely due to its low systemic absorption and its affinity for smooth muscle cell membranes.[19]

In this multinational, double-blind, randomized controlled trial, the authors investigated whether otilonium bromide might have a prolonged therapeutic effect following its discontinuation. Included in this study were a total of 356 patients with diarrhea, constipation, or mixed IBS who experienced at least 2 episodes of abdominal pain per week during a 2-week placebo run-in period. After the run-in period, patients were randomized to receive either 40 mg of otilonium bromide (n=179) 3 times daily or a placebo (n=177) for 15 weeks. During the 15-week treatment phase and a 10-week post-treatment phase, patients had weekly evaluations for the primary endpoint, which was the frequency (on a 4-point categorical scale) and intensity (verbal rating scale) of abdominal pain. In addition, patients were assessed for secondary endpoints including bloating severity, stool patterns, global treatment efficacy (GTE) assessments by patients and investigators, quality of life, and adverse events.

Otilonium bromide significantly reduced the frequency of abdominal pain episodes (-0.90±0.88 vs -0.65±0.91; P=.03), bloating severity (-1.15±1.16 vs -0.91±1.12; P=.02) and patient GTE assessment (1.29±1.08 vs 1.04±1.14; P=.04). It was well tolerated with an adverse event profile similar to that of the placebo. Of the 356 patients who participated in this study, 83 patients treated with otilonium bromide and 80 patients given a placebo reported fewer than 2 episodes of abdominal pain per week during the last 2 weeks of the treatment phase and were eligible for follow-up. Post-treatment symptom relapse was significantly lower for patients who had taken otilonium bromide compared to those who were given a placebo (10.4% vs 27.2%, respectively; P=.009). A follow-up survival analysis showed that patients given otilonium bromide had a significantly higher probability of remaining relapse-free compared to those who received a placebo (P<.04). GTE assessments by patients (P<.01 at 3 and 6 weeks) and physicians (P<.001 at 3, 6, and 10 weeks) were also better for otilonium bromide than for the placebo. Overall, the findings from this study indicate that otilonium bromide is safe and effectively reduces abdominal pain frequency and bloating severity in patients with IBS.

Table 2. Mean Change from Baseline in Trial Endpoints: Results From 2 Phase III Trials (ITT Population)

Parameter (scale)	Trial 01 (n=630)			Trial 303 (n=642)		
	Placebo (n=215)	LIN 133 µg (n=213)	LIN 266 µg (n=202)	Placebo (n=209)	LIN 133 µg (n=217)	LIN 266 µg (n=216)
CSBMs/week	0.6	2.0 (*P*<.0001)	2.7 (*P* <.0001)	0.5	1.9 (*P* <.0001)	2.0 (*P* <.0001)
SBMs/week	1.1	3.4 (*P* <.0001)	3.7 (*P* <.0001)	1.1	3.0 (*P* <.0001)	3.0 (*P* <.0001)
Stool Consistency (BSFS: 1=hard stool, 7=watery)	0.6	1.8 (*P* <.0001)	2.0 (*P* <.0001)	0.6	1.9 (*P* <.0001)	1.8 (*P* <.0001)
Straining (1=not at all, 5=extreme amount)	-0.6	-1.1 (*P* <.0001)	-1.2 (*P* <.0001)	-0.5	-1.1 (*P* <.0001)	-1.2 (*P* <.0001)
Constipation Severity (1=none, 5=very severe)	-0.3	-0.9 (*P* <.0001)	-1.0 (*P* <.0001)	-0.3	-0.9 (*P* <.0001)	-0.8 (*P* <.0001)
Abdominal Discomfort (1=none, 5=very severe)	-0.3	-0.5 (*P* =.0006)	-0.5 (*P* =.0001)	-0.3	-0.5 (*P* =.0003)	-0.4 (*P* =.0063)
Bloating (1=none, 5=very severe)	-0.2	-0.4 (*P* =.0005)	-0.5 (<0.0001)	-0.2	-0.5 (<0.0001)	-0.4 (0.0049)

BSFS=Bristol stool form scale; CSBM=complete spontaneous bowel movements; ITT=intent-to-treat; LIN=linaclotide; SBM=spontaneous bowel movement.

Linaclotide for IBS

286: Efficacy and Safety of Once Daily Linaclotide Administered Orally for 12-Weeks in Patients With Chronic Constipation: Results From 2 Randomized, Double-Blind, Placebo-Controlled Phase 3 Trials[20]

Anthony Lembo, Harvey Schneier, Bernard J. Lavins, Steven J. Shiff, James E. MacDougall, Xinwei D. Jia, Caroline B. Kurtz, Mark G. Currie, Jeffrey M. Johnston

A recent phase IIb study reported that linaclotide, an oral, first-in-class, minimally-absorbed, guanylate cyclase type-C receptor agonist, improved bowel and abdominal symptoms while providing global symptom relief and an improved quality of life to patients with chronic constipation.[21] Based on these findings, 2 double-blind, phase III trials (01 and 303) were designed to expand these data by evaluating the efficacy and safety of linaclotide in 1,272 patients with chronic constipation. Patients included in these studies met modified Rome II standardized criteria for chronic constipation and had fewer than 3 complete spontaneous bowel movements (CSBM) per week and no more than 6 SBMs per week during a 2-week baseline period.

During the randomization phase, patients received either 133 µg of linaclotide, 266 µg of linaclotide, or a placebo once daily for 12 weeks. All 1,272 patients in the ITT population had at least 1 assessment for the primary endpoint, which was the proportion of CSBM overall responders, defined as having 3 or more CSBM with an increase of 1 or more CSBM from baseline, for 9 weeks or more of the 12-week treatment phase. Both trials achieved the primary endpoint at the 133 µg and 266 µg doses of linaclotide (Trial 01, 16.0% and 21.3% vs 6.0% for PBO [*P*=.0012 and *P*<.0001]; Trial 303, 21.2% and 19.4% vs 3.3% for PBO [both *P*<.0001]). All secondary endpoints were also statistically significant (Table 2). Treatment responses first occurred during week 1 and were sustained over the 12-week treatment period. Although the most commonly reported adverse event was diarrhea, which occurred in a higher proportion of patients receiving linaclotide versus placebo in both trials (Trial 01, 17% vs 3%; Trial 303, 13% vs 7%, respectively), few patients discontinued therapy due to diarrhea (Trial 01, 5% vs 1%; Trial 303, 3% vs 1%, respectively).

From the data presented in these 2 phase III trials, the investigators concluded that linaclotide significantly improved bowel and abdominal symptoms, as well as the severity of constipation in patients with chronic constipation. However, linaclotide use also was associated with diarrhea, which was the most commonly reported adverse event in both trials.

Psychological Stress Predicts the Development of IBS

730: Psychological Distress Predicts Developing New Functional Gastrointestinal Disorders (FGIDs) Among Healthy Community Subjects: a 12-Year Prospective, Population-Based Cohort Study[22]

Natasha A. Koloski, Michael Jones, Jamshid S. Kalantar, Martin D. Weltman, Jessa Zaguirre, Nick Talley

Although the causes of functional gastrointestinal disorders (FGIDs) remain unknown, several etiologic factors have been proposed. Some investigators suggest that multiple causes may be at play including not only biological but also psychological factors. With regard to psychological stress in FGID, chronic daily stress[23,24] and stressful life events[25,26] have been suggested as possible causes of FGIDs. Two studies have supported this hypothesis by demonstrating that stress alters intestinal functioning through disruption of the autonomic nervous system, immune system, and hypothalamic-pituitary-adrenal axis.[25,27] Additionally, the subjective level of stress felt by individuals has been reported to be the most important factor in predicting FGID onset, including changes in IBS symptoms.[28,29] However, establishing a causal relationship between psychological factors and FGIDs has been difficult, and at times, contradictory. Koloski and colleagues note that studies that have examined psychological factors in FGID onset have limitations that dampen their impact. For example, many are retrospective, have inadequate follow-up times or potential sample bias, and limit their focus to only 1 type of FGID.[22] To address these issues, the authors conducted a 12-year longitudinal, prospective, population-based follow-up cohort study to determine whether psychological factors play a role in FGID development.

In designing this study, the authors hypothesized that study participants who did not report having an FGID but reported high levels of psychological distress in 1997 should have an increased risk of having a FGID according to Rome II criteria in 2009. In 1997, 1,175 individuals from Penrith, Australia responded to a validated survey and agreed to be contacted for future research. Of the initial survey responders, 64% (n=1,004) completed the 12-year follow-up survey in 2009. The original and follow-up surveys included standardized questions allowing for Rome II diagnoses to be made for 18 FGIDs. Parameters measured included psychological distress stemming from anxiety and/or depression (by using the Delusions Symptom States Inventory [DSSI] scale) and medication use for stomach and bowel symptoms during the 12-year study period.

In 1997, 591 participants were considered healthy because they did not meet Rome II diagnostic criteria for any of the FGIDs evaluated. However, 12 years later, 35% (n=207) of these participants had developed FGIDs including functional abdominal bloating (11%), functional heartburn (11%), IBS (6%), and functional dyspepsia (4%). To determine whether psychological factors influenced FGID onset in these participants, the investigators compared the levels of anxiety and depression reported by the patients in 1997 and at the 12-year follow-up (ie, 2009). Having significantly higher anxiety levels in 1997 (OR per 5-point change in scores on the DSSI scale, 1.59; 95% CI, 1.11–2.26; P=.01) was found to be a significant predictor of diagnosis of a FGID in 2009, even after controlling for age, gender, and medication use for GI symptoms. FGIDs that correlated with high anxiety at baseline were functional abdominal bloating (OR, 1.62; 95% CI, 1.04–2.52; P=.03) and functional dyspepsia (OR, 2.86; 95% CI, 1.62–5.08; P≤.001). Notably, only functional dyspepsia remained an independent predictor for FGIDs 12 years later (OR, 2.64; 95% CI, 1.44–4.84; P=.002). In addition to anxiety, higher levels of depression at baseline also was a significant independent predictor of functional dyspepsia at follow-up (OR, 2.51; 95% CI, 1.28–4.93; P=.007) but was not significantly associated with the development of any other FGIDs. Taken together, these findings suggest that psychological factors, such as anxiety and depression, may have causal relationships with FGIDs. Further research on this topic is warranted.

Obesity and IBS

782: Obesity: a New Prognostic Factor in the Management of Functional Gastrointestinal Disorders in Children[30]

Silvana Bonilla, Deli Wang, Peter L. Lu, Miguel Saps

A relationship between childhood obesity and FGIDs has been suggested but is poorly understood. Pediatric studies on this topic are limited but data from studies in adults indicate that body mass index (BMI) is associated with abdominal pain and diarrhea, whereas a healthy diet and exercise are associated with fewer GI symptoms.[31] In addition, morbidly obese adults have reported GI symptom relief in the months following certain types of gastric bypass surgery,[32] indicating that higher weights and/or BMIs may be associated with GI discomfort. However, the causal relationship between obesity and FGIDs has not been fully explored, and whether obesity impacts the

prognosis of children with FGIDs is unclear. Furthermore, whether obesity affects FGID treatment outcomes in children is unknown. Therefore, Bonilla and colleagues investigated how obesity impacts treatment response for abdominal pain–related FGIDs in children.

The authors reviewed medical records from pediatric patients diagnosed with functional abdominal pain and IBS according to the Rome III criteria between January 2007 and June 2008. Demographic information including age, sex, race, ethnicity, weight, height, and BMI were noted. Patients were considered obese if their BMI was at or above the 95th percentile for children of the same age and gender. Investigators contacted patients by phone 12–15 months after the initiation of standard FGID medical care and were asked to complete a validated questionnaire that evaluated GI symptoms according to the Rome III criteria. To analyze patient responses, a Fisher exact test was used to determine whether an association between obesity and GI symptoms existed in the study population. In addition, the authors used a Cochron-Mantel-Haenszel test and Cochran-Armitage test (SAS 9.1 software) to calculate mean score differences and to identify trends of clinical symptoms in groups of children who were and were not obese.

The study included a total of 140 patients (mean age, 13.96 years +/-3.46 years) diagnosed with either IBS (64%) or functional abdominal pain (36%). At the time of their FGID diagnosis, 21% of study participants were obese (BMI, 29.69 +/- 5.28), including similar numbers of girls and boys. At follow-up, 60% of all patients contacted reported abdominal pain and 40% had no symptoms. The investigators found that patients who were considered obese were more likely to have abdominal pain (P<.0001), higher pain intensity (P=.0002), and higher pain frequency (P=.0032) at follow-up than patients who were not obese. Obesity also appeared to affect quality of life because patients who were obese were more likely to miss school (P<.0001) and experience disruption of their daily activities (P<.0001) relative to patients who were not obese. Although gender did not affect patient prognoses, boys who reported abdominal pain at follow-up were more likely to be obese than female patients (OR, 3.06; 95% CI, 1.19–7.84; P=.0178). In conclusion, the authors found that obesity at the time of FGID diagnoses is associated with poor treatment outcomes in pediatric patients. They noted that obesity also may affect the persistence of GI symptoms and disability in children with abdominal pain–related FGIDs.

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Commentary

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This year at DDW, there were a number of important abstracts presented that relate to significant advances in the area of irritable bowel syndrome (IBS). This is particularly true for studies that advance the treatment of IBS. In this commentary, I will discuss the importance of the selected works for their relevance in clinical practice. This commentary will be divided into sections based on the area of investigations.

Bacteria and Their Products in IBS

While in research, IBS is defined by the presence of abdominal pain or discomfort; frequently the most bothersome symptom of IBS is gas and bloating. However, this symptom has been most frustrating to treat. Over the last decade, data have accumulated to suggest that bacteria and their products may contribute to IBS symptoms, including gas and bloating. In the first of 3 abstracts related to this topic, Tack and associates report the results of a double-blind randomized controlled trial using AST-120 for the treatment of nonconstipated IBS. Activated charcoal has been used for years as an adsorbent of gas and toxins in the gut (as in the treatment of medication overdoses).[1] AST-120 is a novel porous adsorbent with high surface area. This product is believed to adsorb bacterial toxins and bile acids that may be contributing to symptoms in IBS. In this randomized controlled trial, over an 8-week period, 21% of IBS subjects responded to therapy compared to 11% given placebo. Interestingly, the most responsive symptom was bloating severity. The most significant issue with this product is its palatability. The texture of the product is that of ingesting large sand particles. Although very intriguing, this novel therapy is not yet available in North America.

The second abstract in this category relates to the use of antibiotics in IBS. It was almost exactly a decade ago that initial studies began to describe the effect of antibiotics in IBS.[2] This work generated a hypothesis that bacterial overgrowth is common and may be a cause of symptoms in the majority of IBS patients.[3] While this approach had been controversial due to its contrast to existing psychologic and stress models of IBS, multiple randomized controlled trials continued to demonstrate the benefit of antibiotics.[4-7] The decade has culminated in the 2 pivotal phase III studies (TARGET 1 and TARGET 2) from this year's DDW, examining the effect of a non-absorbed antibiotic, rifaximin, in IBS. Rifaximin at a dose of 550 mg tid produced a greater response in IBS compared to placebo in the primary outcome of both studies. In addition, secondary endpoints of bloating, pain, and stool consistency were also significantly better than placebo. While the benefits seen with rifaximin over placebo are similar to effects seen with other therapies, what most discriminated the antibiotic approach in IBS is that the effect is durable. In these 2 phase III studies, a 14-day course of rifaximin produced a benefit that lasted for 10 weeks (the entire follow-up period of the study). This finding suggests that rifaximin is affecting a pathophysiologic process in IBS. This durablility has never been demonstrated in pharmacologic therapies previously approved for treatment of IBS.

In another interesting abstract, Chou and associates described the workup of IBS patients who did not respond well to antibiotic therapy in IBS. What this abstract describes is the potential change in referral pattern for patients to the tertiary care medical center for IBS management. With the increasing use and success in the treatment of IBS with antibiotics in the community, the referral pattern to tertiary care is changing. Subjects referred to the tertiary care center often now include IBS subjects who either failed antibiotics or have a short duration of response to antibiotics. In this study, the work of these poorly responsive subjects suggests alternative diagnoses that are common in these subjects. Approximately one quarter of subjects had another diagnosis that is often a cause of bacterial overgrowth and positive breath test or another disease altogether. This finding is important since it should alert clinicians to be vigilant in these cases and encourage a thorough consideration of other diagnoses besides IBS.

Other Pharmacologic Therapies in IBS

The next abstract demonstrates the effect of a novel agent that acts as a smooth muscle relaxant. A longstanding therapeutic class of agents in IBS has been the antispasmodics. While use of these agents has been widespread, their efficacy has been questioned.[8] The challenge with these agents is the relative paucity of controlled data and

studies that suggest lack of efficacy. This study is a rare controlled trial of a calcium L-type channel-blocking agent, otilonium bromide. This study is unique in that it examined 356 nonsegregated IBS subjects and demonstrated improvement in a global treatment effect, bloating, and pain. This is one of a very short list of studies of high quality to examine these agents in IBS. While this was a multinational study, the drug is not available in the United States to date.

In another abstract, a new agent in the treatment of constipation was assessed. While this was not a study of constipation IBS, it may have implications in the treatment of this disease state as this is an are of unmet need, given the recent removal of tegaserod from most markets. The agent is a guanylate cyclase type-C receptor agonist, and the effect of this agent is to increase bowel fluid content. In the 2 double-blind studies described in this abstract, there was an improvement noted in constipation. Both trials had success with their primary endpoints at both doses of study (133 µg and 266 µg). Diarrhea (as would be expected) was a common side effect. This drug may be useful in patients with constipation-predominant IBS to mitigate their constipation symptoms.

Psychologic Factors and IBS

The relationship between psychological factors and IBS has mostly been associative. In other words, patients referred for their IBS to tertiary care medical centers have a higher prevalence of psychological events in their past. These include physical and/or sexual abuse and other psychological problems. However, large-scale studies of patients in the community have been less confirmatory of the association.[9] To date, the only conclusive cause of IBS has been acute gastroenteritis.[10] This is referred to as post-infectious IBS. The prospective study of outbreaks of gastroenteritis in the community and subsequent meta-analyses of these data confirm that IBS is precipitated by these acute infections. In the case of psychological trauma, there are no clear prospective studies. In abstract 730, Koloski and associates administered a questionnaire to subjects in 1997 and identified those with anxiety and those with depressive symptoms. Twelve years later, they were re-evaluated for the presence of functional symptoms. This was a relatively large study of over 1,000 subjects. The presence of anxiety in 1997 predicted the development of functional bloating and dyspepsia in 2009. Dyspepsia was the only functional disorder that correlated with a history of depression. While IBS specifically was not seen, this is an important study looking in a prospective technique at the development of functional disease. The problem is that the time lag between 1997 and 2009 limits the ability to directly attribute the functional disorder to the psychological problem. There are many factors in patients with psychological disorders that might differ from controls including socioeconomic status, medications, among others. Unlike post-infectious IBS, which develops weeks to months following intestinal infection, examining 12 years later provides only a vague connection.

Obesity and IBS

There is a great deal of urgency surrounding the research of the growing epidemic of obesity in western countries. While the causes of obesity are multifactorial, certainly the gastrointestinal tract plays a role. In a growing list of studies, subjects with obesity have been shown to have altered bowel habits.[11] In addition, studies suggest that subjects with IBS may also have a propensity for increased body mass index.[12] In this study, children with functional bowel disease were identified. The authors indicate that children with obesity described a greater pain intensity and frequency. At this time, there are only a small number of studies examining the link between obesity and functional disorders. The challenge in this area is that both obese patients and patients with functional disease have abnormal diet patterns. For example, IBS patients often describe avoidance of dairy products. These factors will be vitally important as we continue to explore relationships between IBS and obesity. In addition, there is increased understanding of the role of gut flora in IBS and obesity as well. This link may also need to be explored.

In conclusion, studies have now confirmed the importance of gut flora in IBS based on new large-scale controlled antibiotic studies. While not available as yet, new concept drugs such as guanylate cyclase agonists, antispasmodics, and adsorbents might also be important future therapies for IBS.

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Notes


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